IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Application of: | ) | |
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| Roberts et al. | ) | |
| | ) | Group Art Unit |
| Serial No.: 08/304,147 | ) | |
| | ) | |
| Filed: September 12, 1994 | ) | |
| | ) | |
| Re: Method and Compositions to Assess Oxidative Stress in Vivo | ) | |

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

**INFORMATION DISCLOSURE STATEMENT**

Pursuant to 37 C.F.R. §1.56 and 1.97-1.99, Applicants bring the following patents and publications to the attention of the Patent and Trademark Office. Because copies of all but two of these documents were provided for in the Parent Application, U.S. Serial No. 07/715,419, Applicant has only provided copies of the two documents not disclosed in the parent application. Applicant has listed all of the documents on a PTO 1449 form. If Examiner would like copies of any of these references, the Applicant would be more than happy to supply them.

AR1 Blair et al., Prostacyclin is not a Circulating Hormone in Man, Prostaglandins, 23:579-589 (1982).

AS1 Burk et al., Liver Necrosis and Lipid Peroxidation in the Rat as the Result of Paraquat and Diquat Administration, J. Clin. Invest. 65:1024-1031 (1980).

AT1 Frolich et al., Urinary Prostaglandins, Identification and Origin, J. Clin. Invest. 55:763-770 (1975).

AR2 Halliwell et al., The Measurement of Free Radical Reactions in Humans, FEBS Letters 213 number 1:9-14 (1987).

AS2 Janero, D., Malondialdehyde and Thiobarbituric Acid-Reactivity as Diagnostic Indices of Lipid Peroxidation and Peroxidative Tissue Injury, Free Radical Bio. and Medi. 9:515-540

(1990).

AT2 Levine et al., The Development of a Radioimmunoassay for 12-L-Hydroxyeicosatetraenoic Acid, Prostaglandins 20:923-34 (1980).

AR3 Liston et al. I, Transformation of Prostaglandin $D_2$ to 9∝, 11$\beta$-(15S)-trihydroxyprotsa-(5Z, 13E)-dien-1-oic acid (9∝, 11$\beta$-prostaglandin $F_2$): A Unique Biologically Active Prostaglandin Produced Enzymatically in Vivo Humans, Proc. Natl. Acad. Sci. USA, 82:6030-6034 (1985).

AS3 Liston et al. II, Metabolic Fate of Radiolabeled Prostaglandin $D_2$ in a Normal Human Male Volunteer, J. Bio. Chem. 260:13172-13180 (1985).

AT3 Morrow et al. I, A Series of Prostaglandin $F_2$-like Compounds are Produced in vivo in Humans by a Non-Cyclooxygenase, Free Radical-Catalyzed Mechanism, Proc. Natl. Acad. Sci. USA, 87:938-37 (December 1990).

AR4 Morrow et al. II, Formation of Unique Biologically Active Prostaglandins In Vivo by a Non-Cyclooxygenase Free Radical Catalyzed Mechanism, Clin. Res. 38:464A (April 1990).

AS4 Morrow et al. III, A Stable Isotope Dilution Mass Spectrometric Assay for the Major Urinary Metabolite of $PGD_2$, Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Vol. 21, p. 315 edited by B. Samuelsson et al., Raven Press, New York (October 1990).

AT4 Morrow et al. IV, Formation of Unique Biologically Active Prostaglandins in Vivo by a Non-Cyclooxygenase Free Radical Catalyzed Mechanism, Advances in Prostaglandin, Thromboxane, and Leukotriene Research, Vol. 21, p. 125 edited by B. Samuelsson et al., Raven Press, New York (October 1990).

AR5 Morrow et al. V, Noncyclooxygenase Oxidative Formation of a Series of Novel Prostaglandins: Analytical Ramifications for Measurement of Eicosanoids, Analyt. Bio. 184:1-10 (January 1990).

AS5 Morrow et al. VI, Non-Cyclooxygenase Oxidative Formation of a Series of Novel Prostaglandins: Ramifications for Measurement of Eicosanoids in Biological Fluids, Biological Oxidation Systems, 2:695-708 (November 5, 1990).

AT5 Morrow et al. VII, Abstract - Non-Cyclooxygenase Formation of a Series of Novel Prostaglandins In Vivo in Humans, Enzymes in Prostaglandin and Leukotriene Metabolism (abstract 51 (081-082)), (October 25, 1989).

AR6 Morrow et al. VIII, Abstract - Formation of Unique Biologically Active Prostaglandins in Vivo by a Non-Cyclooxygenase Free Radical Catalyzed Mechanism, Abstract Int'l Conf. on Prostaglandins p. 12, Florence, Italy, May 28, 1990.

AS6 Murphy et al., Preparation of $^{18}O$ Derivatives Eicosanoids for GC-MS Quantitative Analysis, In Method in Enzymology (Lands, W.E.M., and Smith, W.L., Eds.): Academic Press, New York. 86:547-51 (1982).

AT6 Murray et al., Release of Prostaglandin $D_2$ into Human Airways During Acute Antigen Challenge, New Eng. J. of Med. 315:800-804 (1986).

AR7 Porter et al., Peroxy Radical Cyclization as a Model for Prostaglandin Biosynthesis, J. Org. Chem. 40:3614-3617 (1975).

AS7 Prakash et al., Synthesis of the Major Urinary Metabolite of Prostaglandin $D_2$, J. Chem. Society Perkin Trans. I 10:2821-2826 (1988).

AT7 Pryor et al. I, A Suggested Mechanism for the Production of Malonaldehyde during the Autoxidation of

Polyunsaturated Fatty Acids. Nonenzymatic Production of Prostaglandin Endoperoxides during Autoxidation, J. Org. Chem. 40:3615-3617(1975).

AR8 Pryor et al. II, Autoxidation of Polyunsaturated Fatty Acids: II. A Suggested Mechanism for the Formation of TBA-Reactive Materials from Prostaglandin-like Endoperoxides; Lipids 11:370-379 (1975).

AS8 Rich et al., The Carbodiimide Method, The Peptides 1:241-61 (1979).

AT8 Roberts et al. I, Prostaglandin, Thromboxane, and 12-Hydroxy-5,8,10,14-Eicosatetraenoic Acid Production by Ionophore-Stimulated Rat Serosal Mast Cells, Biochimica et Biophysica Acta 575:185-192 (1979).

AR9 Roberts et al. II, Quantification of the $PGD_2$ Urinary Metabolite 9∝-hydroxy-11,15-dioxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic Acid by Stable Isotope Dilution Mass Spectrometric Assay. Methods Enzymol. 86:559-70 (1982).

Patents

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| Lawrence | U.S. 4,859,613 |
| David et al. | U.S. 4,376,110 |
| David et al. | U.S. 4,486,530 |

Blair et al. disclose a mass spectroscopy assay for plasma 6-oxo-prostaglandin $F_1$∝. The test confirmed that this prostanoid is not a circulating hormone in man under normal physiological conditions.

Burk et al. disclose the effects of paraquat on rats. Also discussed is the connection between liver necrosis and lipid peroxidation.

Frolich et al. disclose the detection of urinary prostaglandin $E_2$ and $F_2$∝.

Halliwell et al. disclose a method to measure free-radical reactions in humans.

Janero discloses malondildehyde and thiobarbituric acid reactivity as a diagnostic tool to identify lipid peroxidation and peroxidative tissue injury.

Levine et al. disclose an RIA for a prostaglandin.

Liston et al. I disclose the isolation of metabolites of prostaglandin D in human urine. The most abundant metabolite identified was 9, 11 dihydroxy-15-oxo-2, 3, 18, 19 tetranor prost-5-ene-1, 20 dioic acid.

Liston et al. II disclose an assay for 9$\alpha$, 11$\beta$-$PGF_2$ in urine or plasma. It was noted in this article that a patient with systemic mastocytosis had urinary plasma levels of 9$\alpha$, 11$\beta$-$PGF_2$ that were higher than normal circulating levels of this compound.

Morrow et al. I discloses a series of prostaglandin $F_2$-like compounds that are produced <u>in vivo</u> in humans by a noncycloogenase free-radical catalyzed mechanism. Morroe suggest in this article that these compounds may participate as pathophysiological mediators in oxidant injury. Additionally, it is suggested that quantification of these compounds may also provide a noninvasive approach to assess oxidative status in humans. The analysis of the $PGF_2$-like compounds was conducted in urine and plasma.

Morrow et al. II disclose the formation of biologically active prostaglandins <u>in vivo</u> by a noncyclooxygenase free-radical catalyzed mechanism. It is noted that the formation of these compounds is enhanced in situations involving the generation of free radicals. This abstract was discussed at the AFCR/ASCI/AAP meeting, May 6, 1990, in Washington, D.C.

Morrow et al. III disclose a mass spectrometric assay

for the major urinary metabolite of $PGD_2$.

Morrow et al. IV disclose the discovery of $PGF_2$ compounds produced in vivo in human plasma. It is indicated in this paper that these compounds possess potent biological activity. Additionally, it is suggested that the quantification of these prostanoids may provide a noninvasive approach for the assessment of oxidant status in humans.

Morrow et al. V disclose the detection of multiple $PFG_2$ compounds with levels ranging from approximately 5 to 40 pg/ml. It was noted that the concentration of this compound increases during storage.

Morrow et al. VI disclose multiple prostaglandin $F_2$-like compounds in plasma.

Morrow et al. VII disclose multiple prostaglandin $F_2$ compounds in plasma. The author states: "whether these compounds may have relevance as mediators or markers of pathophysiological situations involving oxidative stress at present remains speculative". A manuscript from this conference was published in 1990 and is included as Morrow VI.

Morrow et al. VIII disclose the formation of prostaglandin $F_2$ compounds formed in vivo by a noncyclooxygenase free-radical derived mechanism. The biological activity of 8-epi-$PGF_{2\alpha}$ is discussed.

Murphy et al. disclose a mass spectrometric for assay for an eicosanoid compound.

Murray et al. disclose the relationship between prostaglandin $D_2$ and an acute allergic response.

Porter et al. disclose the conversion of unsaturated lipid hydroperoxides to prostaglandin analogs by free-radical initiators.

Prakash et al. disclose the synthesis of a urinary metabolite of prostaglandin $D_2$.

Pryor et al. I disclose a mechanism for the production of malonaldehyde during the autooxidation of polyunsaturated fatty acids.

Pryor et al. II disclose a method for forming endoperoxides in a free radical cyclization process operating in competition with hydroperoxide formation during the autooxidation of PUFA or their esters containing three or more double bands.

Rich et al. disclose mechanisms of carboxylactivation.

Roberts et al. I disclose the isolation of metabolites of arachidonic acid obtained from rat seronal mast cells in response to stimulation with ionophore A23187.

Roberts et al. II disclose a method to quantify $PGD_2$ urinary metabolite 9∝-hydroxy-11, 15-dioxo-2, 3, 18, 19-tetranorprost-5-ene-1, 20-dioic acid using a mass spectrometric assay.

U.S. Patent No. 4,859,613 discloses immunoassay for glutathione and antibodies.

U.S. Patent No. 4,376,110 discloses an immunoassay technique.

U.S. Patent No. 4,486,530 discloses an immunoassay technique.

If any fees are incurred as the result of the filing of this paper, authorization is given to charge deposit account No. 20-1111.

Respectfully submitted,

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